DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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June 19, 2006

Albert Finch, M.D.
Executive Medical Director
Children's Hospital of the King's Daughters
601 Children's Lane
Norfolk, VA 23507

Robert F. Williams, Ph.D., MBA, Associate Dean
Research Subjects Protection
Eastern Virginia Medical School
P.O. Box 1980
Norfolk, Virginia 23501

RE: Human Research Subject Protections Under Federalwide Assurance FWA- 3171
Research Project: Phase I Trial: Safety and Effectiveness of Four Anti-HIV Drug Combinations in HIV-Infected Children and Teens
Project Number: ACTG #377
Principal Investigator: Thomas T. Rubio, M.D.

Dear Drs. Finch and Williams:

The Office for Human Research Protections (OHRP) has reviewed the Children's Hospital of the King's Daughters' (CHKD) March 30, 2006 response to OHRP's February 17, 2006 letter regarding indications of possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research. OHRP understands that CHKD and Eastern Virginia Medical School (EVMS) are separate entities and that the institutional review board (IRB) that approved the above-referenced study on behalf of both EVMS and CHKD is operated by EVMS.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research.

(1) HHS regulations at 45 CFR 46.111 state that, in order to approve research covered by the regulations, the IRB shall determine that certain requirements are satisfied. OHRP finds that when reviewing this research, the EVMS IRB failed to obtain sufficient

information to make the following determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(a) 45 CFR 46.111(a)(3): Selection of subjects is equitable. In making this determination, IRBs should be particularly cognizant of the special problems of research involving vulnerable populations. In particular, OHRP finds that EVMS IRB records appear to demonstrate a failure of the IRB to obtain sufficient information regarding the selection of wards of the state and foster children as research subjects.

(b) 45 CFR 46.111(a)(4): Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with 45 CFR 46.116. In particular, OHRP finds that EVMS IRB records appear to demonstrate a failure of the IRB to obtain sufficient information regarding the process for obtaining permission of parents or guardians for wards of the state or foster children.

(c) 45 CFR 46.111(b): When some or all of the subjects (e.g., children) are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects. In particular, OHRP finds that EVMS IRB records appear to demonstrate a failure of the IRB to obtain sufficient information regarding such safeguards with respect to the enrollment of wards of the state or foster children.

(2) HHS regulations at 45 CFR 46.404-409 require specific findings on the part of the IRB for approval of research involving children. OHRP finds that EVMS IRB records do not contain sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.404-409.

Corrective Actions: OHRP acknowledges the efforts by your institutions to improve human subjects protections which address these findings. The IRB of EVMS now has practices in place to ensure that the categories of research involving children under HHS regulations at 45 CFR 46.404-407 are appropriately discussed and documented in the IRB minutes. The IRB checklist includes a section entitled "Additional Protections for Children Involved as Subjects in Research," and asks whether the signature block in the consent has been amended to include language indicating that an advocate must be appointed prior to enrolling wards of the state. The IRB checklist also asks whether selection of subjects is equitable. A statement has been added to the IRB approval letter reminding the investigator that the IRB must be contacted and an advocate appointed prior to enrollment of any wards of the state.

OHRP recommends education of IRB staff and investigators regarding the requirements of 45 CFR 46.409 and 46.111. This education should include discussion of the separate roles of legal guardian and advocate, as well as methods for determining these positions. OHRP further notes

that the requirements surrounding wards of the state are not discussed in the EVMS 2003 IRB Standard Operating Procedures, found online; wards of the state are cited only as a vulnerable category without further discussion. OHRP strongly recommends that this document be amended to reflect the requirements of 45 CFR 46.409.

OHRP finds that institution of the corrective actions described above adequately address the OHRP's findings and are appropriate under the CHKD and EVMS assurance. As a result of this determination, there should be no need for further involvement of OHRP in this matter.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Julia Gorey, J.D.
Division of Compliance Oversight

cc: Karen Mitchell, HPA, Children's Hosp King's Daughters/East Va Med Sch
Dr. Barbara Freund, Chairperson, IRB #1, East Va Med Sch
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